Computational Toxicology Research in ORD: The Scientific Foundation for the Paradigm Shift in Chemical Risk Assessments?

USEPA

Office of Prevention, Pesticides, and Toxic Substances

ORD's Computational Toxicology Framework

The Goal

- Use the state-of-the-science to improve risk assessments and reduce uncertainties

The Objectives

- Improve source-to-outcome linkage
- Improve prioritization techniques for testing
- Improve quantitative risk assessments

The Outcome?

- A scientific foundation for the assessment paradigm shift

Computational Toxicology Research

Challenges in Pesticide/Industrial Chemical Risk Assessments

Scientific Outcomes to Meet the Challenges

An Opportunity to Enable a Paradigm Shift to Hypothesis-Driven Assessments

The Challenge for TSCA and FIFRA/FQPA: A Sustainable Risk Assessment Process

Given finite resources and time to generate and evaluate data,

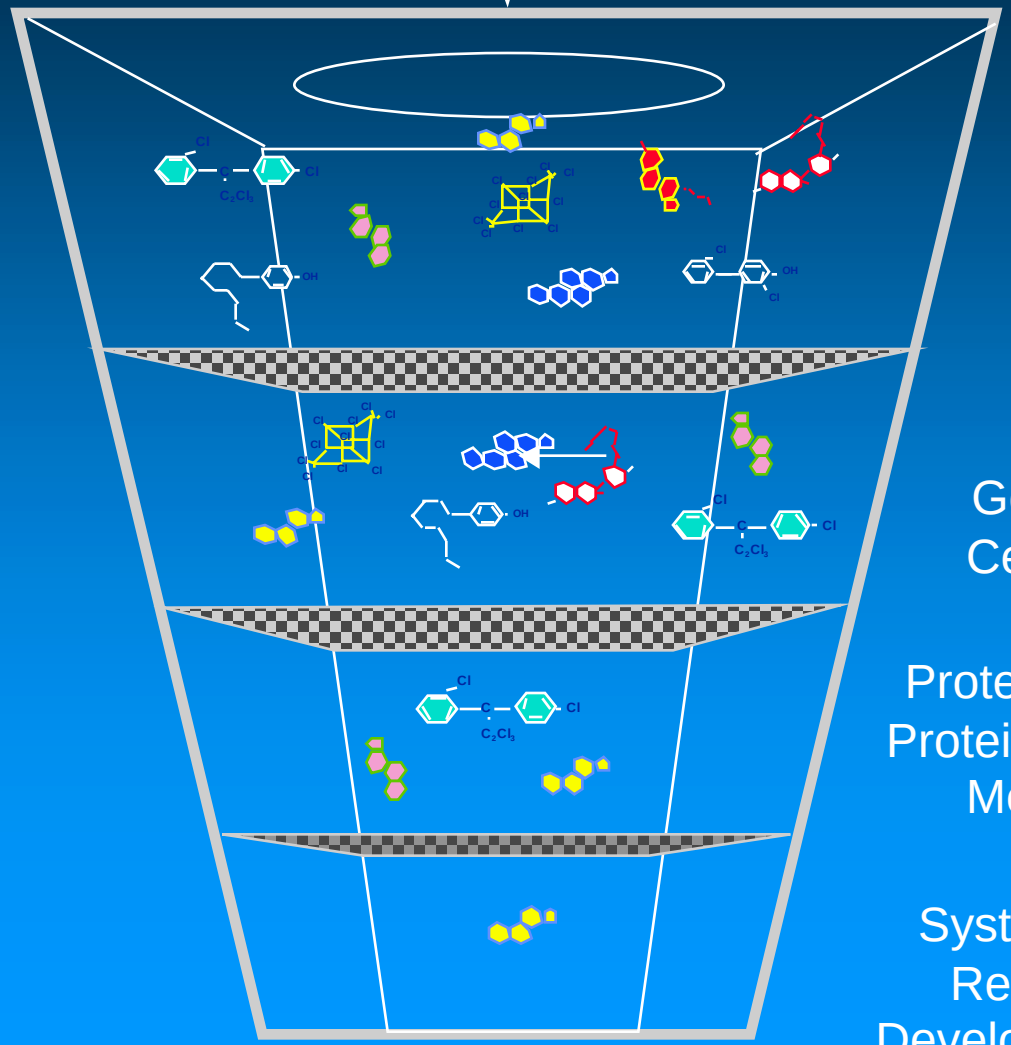
When confronted with large numbers of chemicals to assess, which chemicals to evaluate first for a given adverse outcome?

When confronted with many potential adverse outcomes for a given chemical, which outcomes are more likely?

Identifying Toxicological Potential

TSCA & FIFRA Inventories

Ranking & Prioritization: Screening Assays



Testing

Partitioning; Electrophilicity; Redox Cycling

Gene Activation; Cellular Function

Protein Inhibition; Protein Production; Metabolism

Systemic effects, Reproduction, Development, Cancer

Existing Data and Models

A TSCA Challenge: The HPV Program

- High Production Volume (HPV) Chemicals - 2,800 chemicals that are produced or imported at levels of one million pounds or more/year
- Industry asked in 1998 to volunteer to make hazard data publicly available and generate new data as appropriate
- Data set adequate to allow screening level hazard characterization

Hazard Endpoints Covered

Physicochemical properties: melting & boiling pts., vapor pressure, water solubility, partition coeff.

Environmental fate: photodegradation, stability in water, biodegradation, transport (model)

Environmental effects: acute toxicity in fish, aquatic invertebrates and aquatic plants

Health effects: acute and subchronic toxicity, genetic toxicity, reproductive and developmental toxicity

Results to Date: Submissions On Web

(http://www.epa.gov/chemrtk/volchall.htm)

(As of 8/26/03)

239 Submissions (1072 chemicals)

96 Categories (929 chemicals)

143 Individual chemicals

(Majority of chemicals in the HPV Challenge Program belong to a category (87%))

Types of Chemical Categories

- Traditional
  --Common functional group
  --Incremental change in chain length
  --Metabolic series
- Production streams
  --Petroleum products
  --Sequential change in composition
- Mixture families
  --Family of similar substances

Good Categories Should Follow a Pattern

- Individual chemicals in a category must be related
- An important relationship (for human health endpoints) might be a similar mode of toxic action
- Similar mode of action could be an increase or decrease in potency or severity, but with consistency in target organ/effects
- Thus, patterns should be apparent such that tested category members can inform untested category members

A FIFRA Challenge:
Which Adverse Outcomes are Most Likely?

Conventional Food Use Pesticide Assessment

$15 to 20M to generate full battery of tests

$1M for the Agency to assess test results

5 to 7 years to license

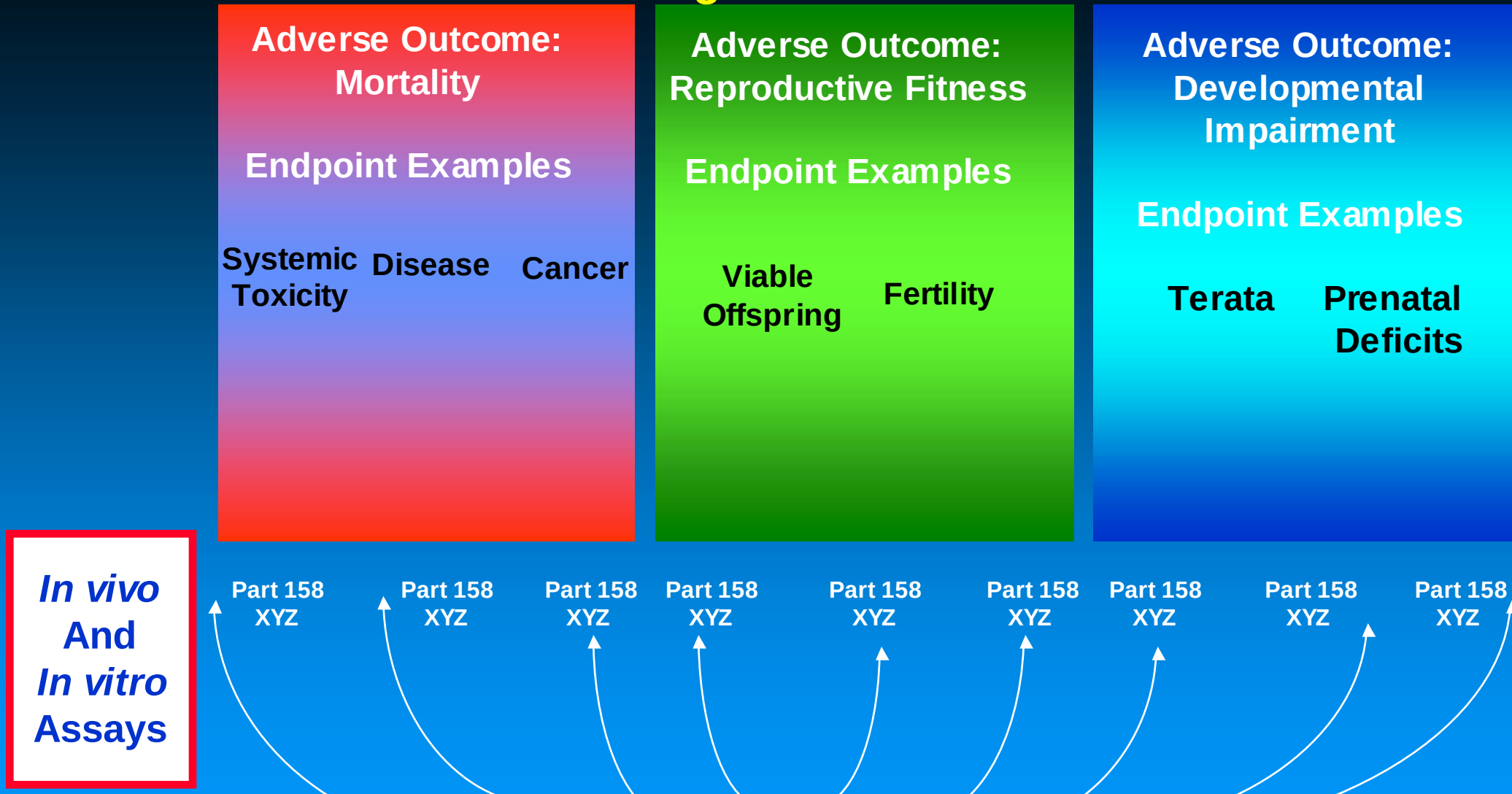
The Challenge of the Current Paradigm

Identifying lower risk active ingredients

Backlog in assessing inert ingredients

Difficulty in prioritizing scarce assessment resources

Risk Management Decisions



Conventional Pesticide/Metabolite

Generate data and then determine relevant effect

Inert Ingredient
Lower Toxicity Pesticide Guidance

Explicit Paradigm Shift in Risk Assessment

Inert Ingredients assessment by 2006 -

700 existing inerts to assess

55 new inerts and counting in the queue

Risk assessment backlog for new and existing active ingredients

Inert Ingredient Lower Toxicity Pesticide Guidance

Explicit Paradigm Shift in Risk Assessment

Screening process based on existing data and models:

- Level 1- Qualitative screen (320 completed)
- Level 2 - Quantitative screen
- Level 3 - Identification of specific tests

The Agency requires sufficient, credible information from which to make a decision, not an overwhelming amount of information.

Risk Management Decisions

Adverse Outcome: Mortality

Endpoint Examples

Systemic Toxicity | Disease | Cancer

Adverse Outcome: Reproductive Fitness

Endpoint Examples

Viable Offspring | Fertility

Adverse Outcome: Developmental Impairment

Endpoint Examples

Terata | Postnatal Deficits

In silico and *In vitro* Analyses (COMP TOX?)

Before

In vivo Assays

Part 158 XYZ

What *in vivo* data , if any, is needed, and why?

Part 158 XYZ

Inert Ingredients / Low Toxicity Actives/HPVs/PMNs

Hypothesis-Driven Approach to Establish Information Needs

The Endocrine Disruptor Screening Challenge

Implicit Paradigm Shift in Risk Assessment

FQPA – Screening and testing program; intended to start in 1998

Tier 1 testing assays expected on line 2005

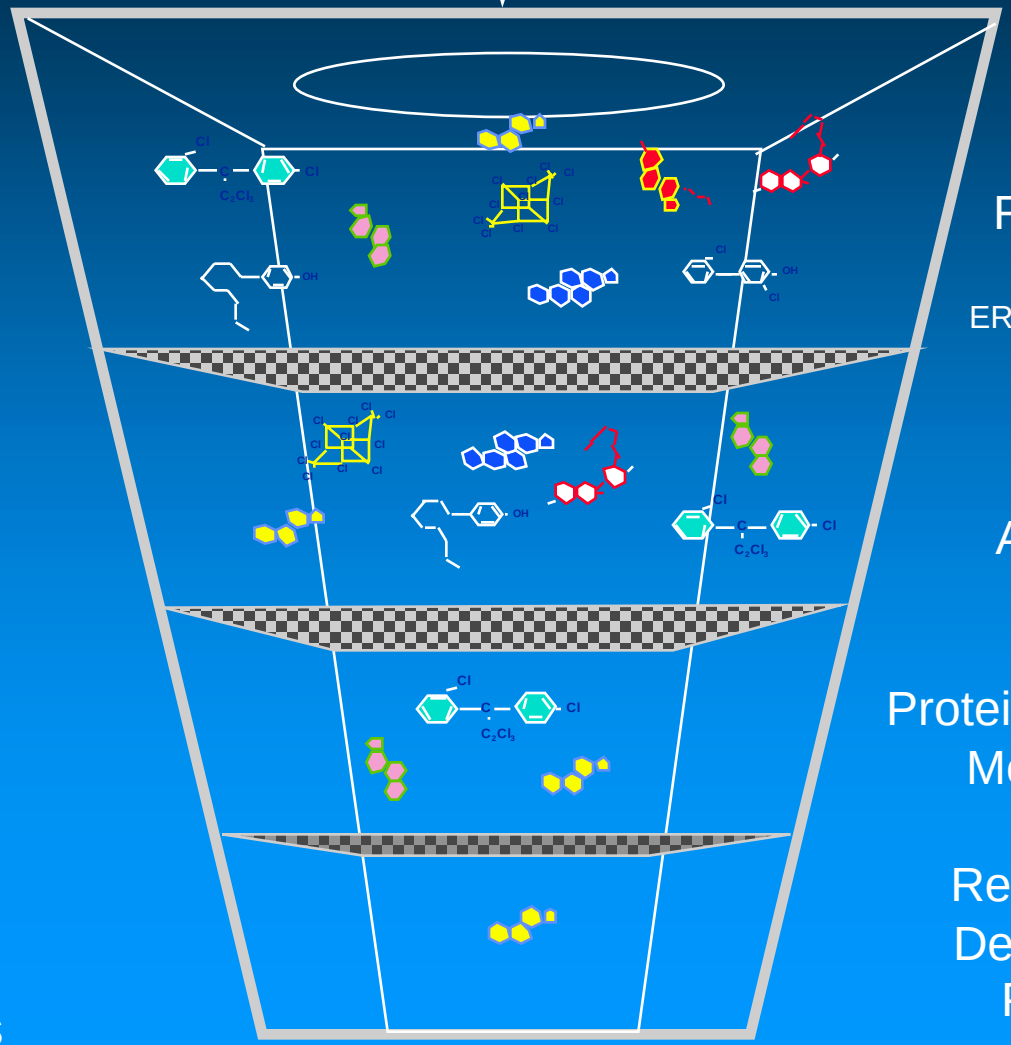
Prioritization and screening techniques unavailable

NRDC agreement requires listing active ingredients/ high production volume inerts end of 2003

Identifying Endocrine Disrupting Potential

TSCA & FIFRA Inventories

Ranking & Prioritization: Screening Assays



Receptor Binding
ER, AR, RXR, etc

Gene Activation

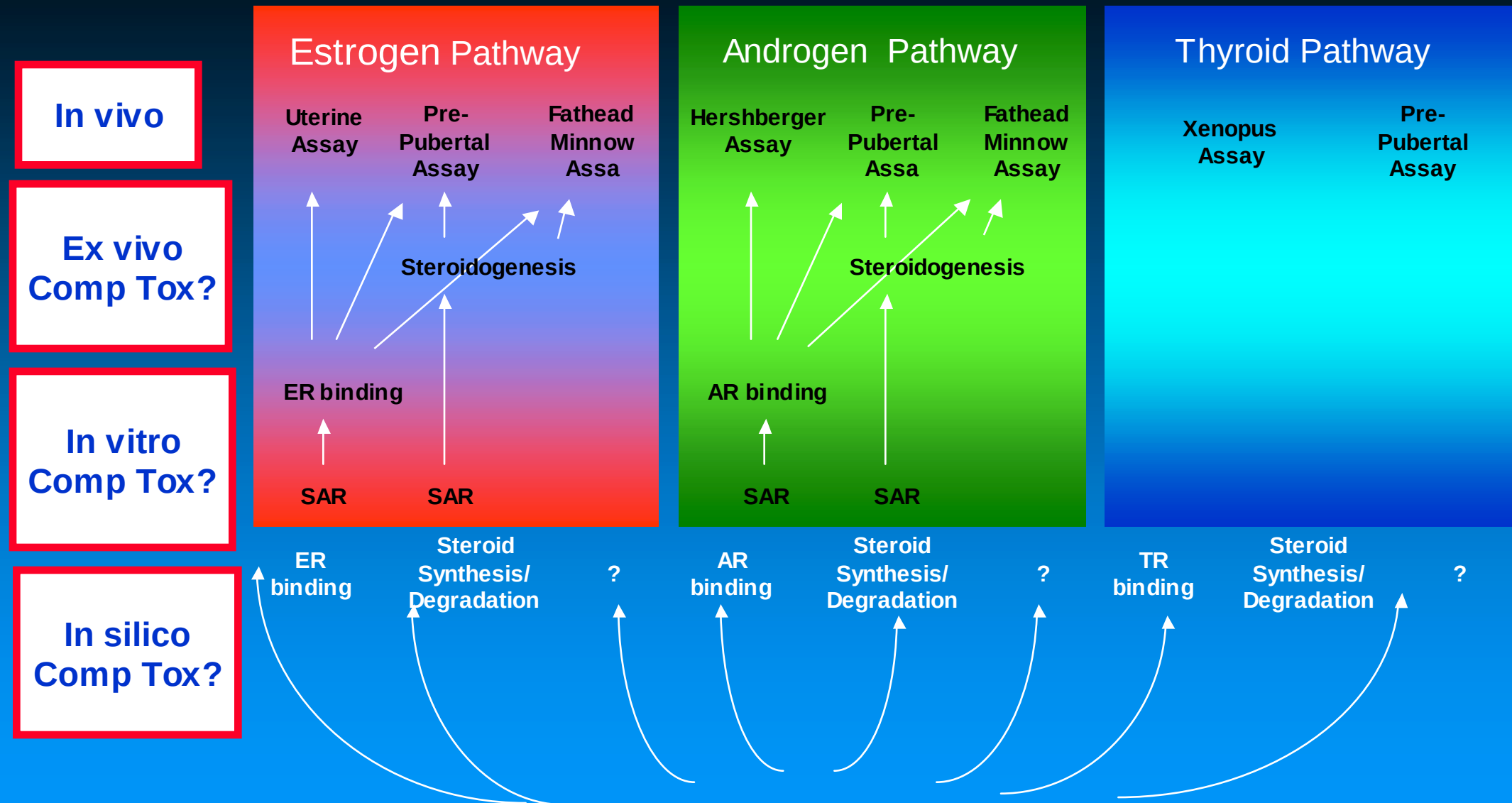
Protein Production; Metabolism

Reproduction, Development, Pathology

Structure Activity Relationships

Tier I and II Testing Assays

REPRODUCTIVE AND DEVELOPMENTAL OUTCOMES



Problem: Among 2000 active ingredients and HPV-inerts, which ones are likely to disrupt which endocrine systems?

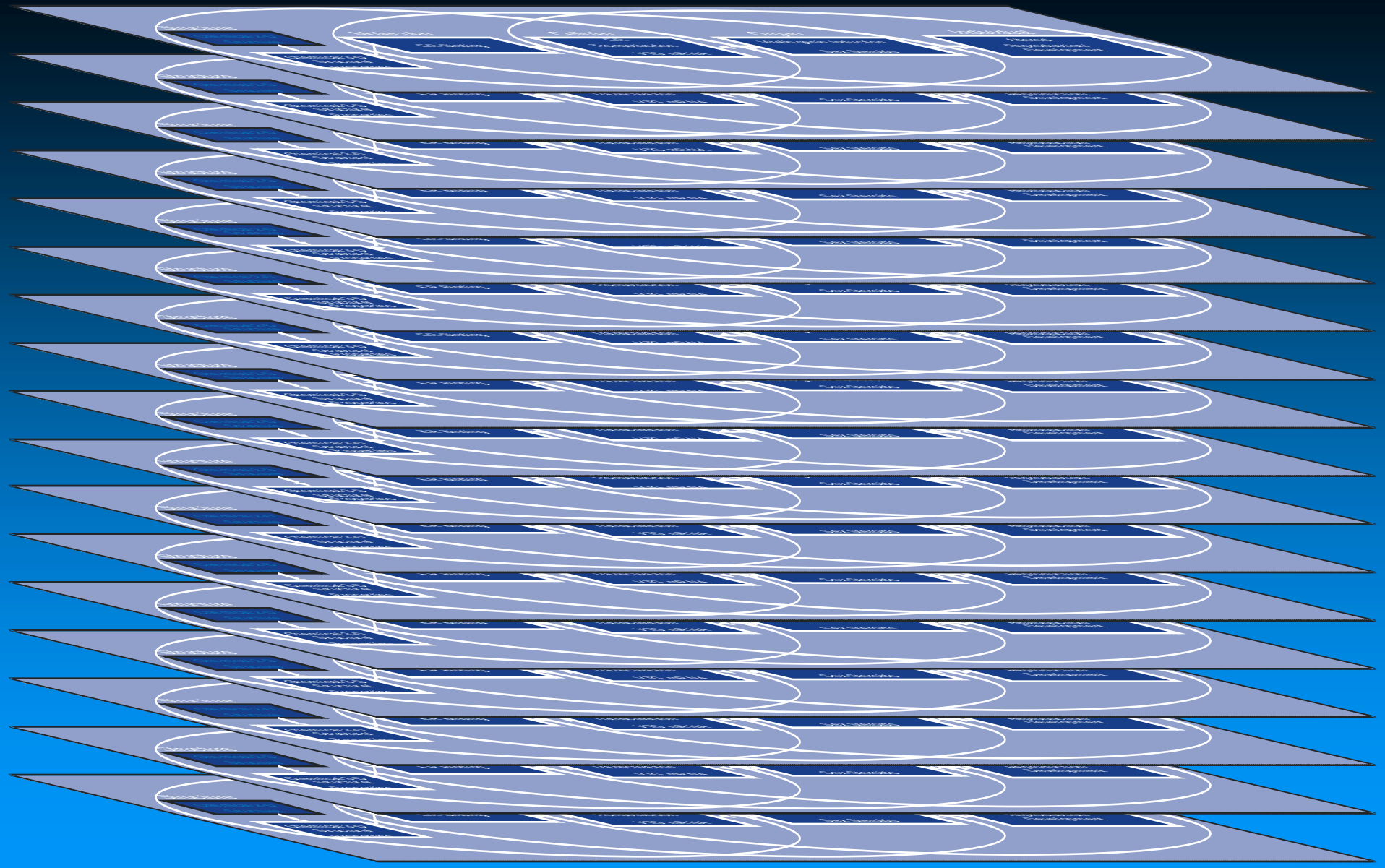
Computational Toxicology Priorities: Getting Started – Building Momentum

In silico and *in vitro* effects models to support a hypothesis-driven risk assessment process – the new paradigm

Toxicity pathways; chemical metabolism and metabonomics are the foundation to the framework

Elucidating toxicity pathways and metabolism addresses problem formulation/hazard identification needs and provides the context for prioritizing future research and implementation

Mapping Toxicity Pathways to Adverse Outcomes



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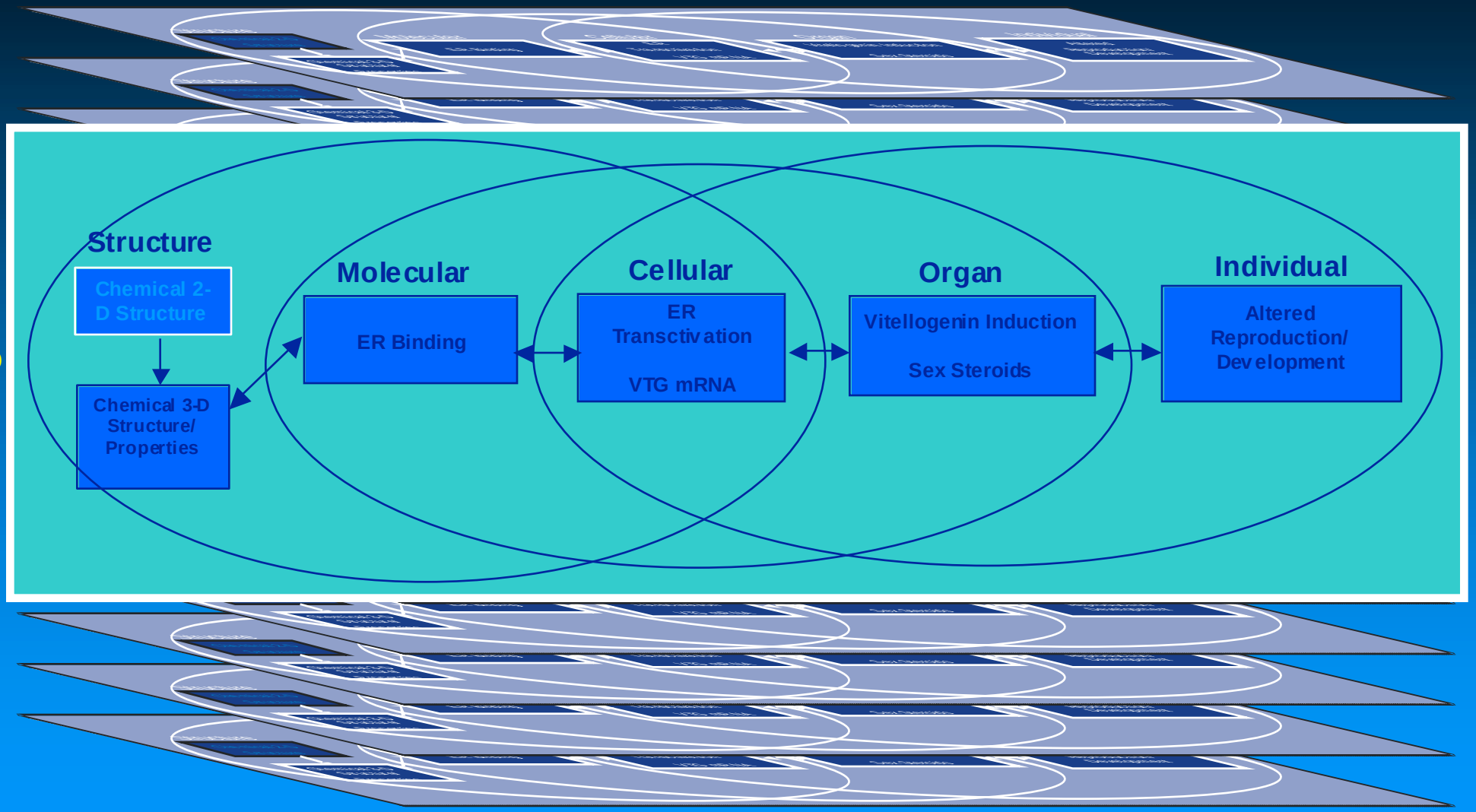
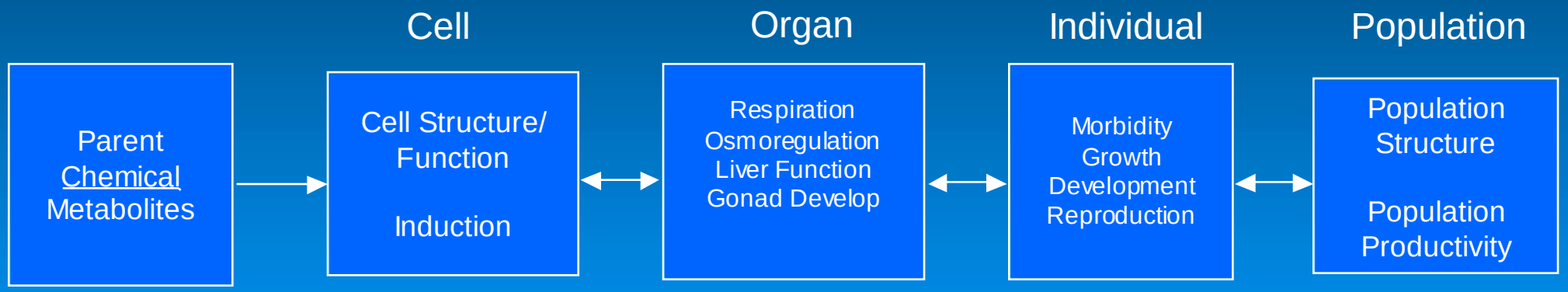


Pesticide/Industrial Chemical Risk Assessments

Linkage and Focus Across Levels of Biological Organization

COMPUTATIONAL TOXICOLOGY

Initial Emphasis



Optimizing Resources, Costs, and Time in Generating and Evaluating Information

Understanding

Relevance

Computational Toxicology Outcomes: Indicators of Success

In silico and *in vitro* endocrine disruptor screening techniques employed by the Agency at the end of FY05 to inform Tier I *in vivo* testing strategy

The Agency's PMN, HPV, inert ingredient and lower toxicity pesticide risk assessment process employs first generation *in silico* and *in vitro* techniques derived from the Computational Toxicology effort by FY06

By achieving these outcomes, ORD establishes itself as a scientific leader in providing the means to employ a new assessment paradigm, which ensures society's resources are focused on those chemicals and potential effects of greatest likelihood and concern.